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COOPERATIVE STUDIES

Improved Infarct-Related Arterial Patency After High Dose, Weight-Adjusted, Rapid Infusion of Tissue-Type Plasminogen Activator in Myocardial Infarction: Results of a Multicenter Randomized Trial of Two Dosage Regimens

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To determine whether a weight-adjusted high dose (2 mg/kg body weight over 3 h) rapid infusion of recombinant tissue-type plasminogen activator (rt-PA) was more efficacious than a weight-adjusted standard dose (1.25 mg/kg over 3 h) in achieving reperfusion in the setting of acute myocardial infarction, 175 patients were entered into a randomized multicenter trial. Eighty-four patients were entered into the high dose group, receiving 1.2 mg/kg (10% given as a bolus injection) over 1 h, followed by 0.8 mg/kg over the next 2 h. Ninety-one patients were given 0.75 mg/kg (10% given as a bolus injection) in 1 h, followed by 0.5 mg/kg administered over the next 2 h. The median dose in the group that received 2 mg/kg dose was 145 mg, compared with 100 mg in the group that received 1.25 mg/kg.

The 90 min patency rate in the group that received 2 mg/kg was 84% compared with 70% in the group that received 1.25 mg/kg ($p = 0.003$). Sixty-four percent of the patients in each group underwent coronary angioplasty at the time of cardiac catheterization. The infarct-related artery patency rate at the end of catheterization was 91% in the group that received 2 mg/kg compared with 83% in the group that received 1.25 mg/kg ($p = 0.08$). Among patients with a patent infarct-related coronary artery after catheterization, the 6 month mortality rate in the group that received 2 mg/kg was 2.9% compared with 9.8% in the group that received 1.25 mg/kg ($p = 0.15$). The bleeding complication rate in the two groups was similar. Two patients in the group that received 2 mg/kg developed nonfatal intracranial bleeding (one after emergency open heart surgery).

These data suggest that more rapid administration of a higher weight-adjusted dose of rt-PA may be more effective in restoring infarct-related artery patency in the setting of acute myocardial infarction than the currently accepted dose of 100 mg over 3 h. Larger randomized trials are warranted to evaluate the need for prolonged (>60 to 90 min) infusions, optimal dosage and the risk of intracranial bleeding with more rapid rt-PA administration.

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As interventional therapy in acute myocardial infarction has evolved, it has become apparent that acute infarct-related coronary artery patency after successful thrombolytic intervention is associated with both improved long-term left ventricular function and survival (1,2). The Thrombolysis in Myocardial Infarction (TIMI) Trial (3) suggested that intravenous recombinant tissue-type plasminogen activator (rt-PA) was more effective than intravenous streptokinase in restoring patency to the infarct-related artery in the setting of acute myocardial infarction. In another multicenter randomized study (4), intravenous rt-PA resulted in infarct-related artery patency in approximately 70% of patients and

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was comparable in efficacy with intracoronary streptokinase.

Concomitant use of coronary angioplasty in addition to intravenous rt-PA produces a slightly higher immediate patency rate, but does not affect recovery of left ventricular function and may be associated with lower survival rates (5,6). Therefore, improved infarct-related artery patency obtained with lytic agents or combinations of lytic agents in addition to anticoagulant and antiplatelet agents is desirable. A report (7) of a small series of patients suggested that the infusion rate of rt-PA correlated with rt-PA levels and that higher infusion rates correlated with higher infarct-related artery patency rates.

The TIMI investigators (8) demonstrated that increased rt-PA infusion doses were associated with higher reperfusion rates, mild increases in fibrinogen depletion and accelerated fibrin degradation product generation. However, these investigators believed that higher doses of rt-PA might be associated with an increased risk of intracranial bleeding (8). The Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) investigators found that a higher, weight-adjusted, first hour dose of intravenous rt-PA was associated with improved infarct-related artery patency without an increase in bleeding complications or fibrinogen depletion (9).

To evaluate the hypothesis that a higher, weight-adjusted accelerated infusion of rt-PA over 90 min in acute myocardial infarction would produce a higher patency rate, we performed a randomized multicenter trial assessing the infarct-related artery 90 min patency and bleeding complication rate with two doses of tissue plasminogen activator in acute myocardial infarction.

Methods

Patient selection. Three centers participated in this study and each had institutional review board approval. The study was conducted from April 15, 1986 through July 20, 1987. Inclusion criteria included age between 18 and 75 years; chest pain of at least 30 min duration with characteristics consistent with coronary ischemia; ST elevation on the electrocardiogram (ECG) of at least 0.1 mV in at least two of three inferior leads (II, III, aVF) or at least two precordial leads (V_1 through V_6) or leads I and aVL; and chest pain duration of <8 h before time of treatment. Eight hours was felt to be a reasonable cutoff for enrollment because the major end point was infarct-related artery patency and there was no clearly established time limit for benefit of thrombolysis at the time the trial was conducted. Patients were required to personally give informed consent.

Exclusion criteria included known pregnancy; bleeding disorder or history of significant previous gastrointestinal bleeding; cerebrovascular accident within the past 6 months; major surgery on an internal organ during the previous 14 days; uncontrolled hypertension (diastolic blood pressure >120 mm Hg); dilated cardiomyopathy; prosthetic heart valve; left bundle branch block; previous coronary bypass graft; oral anticoagulant therapy, prolonged cardiopulmonary resuscitation within the previous 2 weeks; severe head or spinal trauma within the past 6 months; or cardiogenic shock (systolic blood pressure <80 mm Hg requiring vasopressor therapy or balloon pump, or both).

Protocol

rt-PA administration and coronary angiography. Patients were randomized by each center to obtain 1) either 1.25 mg/kg of rt-PA (0.75 mg/kg intravenously, with 10% received as a bolus [not to exceed a dose of 75 mg] over the first hour, followed by 0.5 mg/kg over the next 2 h, with a total dose not to exceed 125 mg), or 2) 2 mg/kg (1.2 mg/kg intravenously, with 10% given as a bolus [not to exceed a dose of 100 mg] over the first hour, followed by 0.8 mg/kg over the next 2 h, with a total dose not to exceed 150 mg). Coronary arteriography was performed 45 to 60 min after the start of the infusion, and was used as the first end point, with perfusion or reperfusion defined as TIMI grade 2 or 3 flow (3) in the infarct-related artery. The second end point was an arteriogram performed 90 min after the rt-PA infusion. After completion of the 90 min arteriogram, patients were allowed to have coronary angioplasty if the infarct-related artery remained occluded (TIMI grade 0 or 1) or had a high grade residual stenosis. However, patients were not eligible to receive other thrombolytic agents, and the dosage regimen assigned to the patient was not varied, except to decrease it if there was clinical evidence of significant bleeding before completion of the infusion.

After 90 min of tissue-type plasminogen activator infusion and coronary arteriography (and angioplasty, if performed), patients were taken to the coronary care unit, where they received intravenous heparin to maintain the activated partial thromboplastin time at 1.5 to 2 times the control value. Patients also received aspirin (300 mg/day) and dipyridamole (75 mg every 8 h). Concomitant administration of nitrates, a calcium channel or beta-adrenergic blocker was allowed if clinically indicated.

Angiographic evaluation. Investigators and study coordinators at each center reviewed coronary angiograms obtained at 60 and 90 min for infarct-related artery patency and a consensus opinion was reached. Reperfusion was judged to be successful if the infarct-related artery demonstrated TIMI grade 2 or 3 flow; TIMI grade 0 or 1 flow represented no reperfusion.

Exclusions from patency analysis. Patients whose coronary arteriogram was unsuccessful were excluded from the patency analysis. Seven patients were excluded at the 60 min arteriogram (five who received 2 mg/kg rt-PA and two who received 1.25 mg/kg), and seven were excluded at the 90 min arteriogram (three who received 2 mg/kg and four who

received 1.25 mg/kg). Reasons for exclusion from analysis included failure of arterial access in sufficient time for performance of angiography, presence of hemodynamic or electrical instability at the time scheduled for angiography or uncertainty of infarct-related artery identification (for example, left circumflex versus right coronary artery).

Use of coronary angioplasty after 90 min angiography. The end point of this trial was infarct-related artery patency at 90 min after initiation of treatment. Angioplasty was attempted in patients with evidence of continued ischemia after thrombolysis, failure of thrombolysis or a residual critical stenosis (≥75% by visual estimation irrespective of flow status in the infarct-related artery). At the time the trial was performed, these criteria for coronary angioplasty were considered standard care at the study centers.

Use of coronary artery bypass surgery. Coronary artery bypass surgery was, in general, performed electively in patients who had multivessel disease before hospital discharge. Several patients were treated with bypass surgery emergently after failed thrombolysis or coronary angioplasty, or both. Irrespective of postthrombolytic therapy, all patients were retained in the study group for analysis of mortality and bleeding complications.

Bleeding and hematologic evaluation. Before treatment, a medical history was obtained as well as a blood sample for hemoglobin and blood coagulation factor determination. In addition, hemoglobin and coagulation factor determinations were performed at 8 to 12 and 24 h. Bleeding was characterized according to site of bleeding and severity. Minor bleeding was described as not clinically significant, not requiring transfusion and <250 ml estimated blood loss. Moderate bleeding was considered to be 250 to 500 ml observed blood loss. Severe bleeding was >500 ml estimated blood loss that required transfusion replacement. Life-threatening bleeding was considered to be intracranial or gastrointestinal bleeding or other internal or external bleeding causing hypotension.

Statistical analysis. The sample size of 175 patients was chosen to detect a difference in reperfusion success at the 95% confidence level on the 90 min angiogram. Patient baseline characteristics (age, weight, time from onset of pain to treatment, gender and infarct-related artery) in the two groups were compared. Mean values for continuous variables were compared with the *t* test, and frequencies for categoric variables were compared between groups with the chi-square test. The primary outcome variable, patency at 90 min measured by coronary angiography, was compared between the two dosage regimens with the chi-square test. Subgroup analyses based on time from onset of pain to treatment and age versus patency were conducted with use of the chi-square test for trend, as appropriate. Confidence intervals for patency rates were calculated by using the normal approximation to the binomial, with continuity correction. Mortality rates were compared with use of Fisher's exact test.

Table 1. Patient Baseline Characteristics*

	1.25 mg/kg Dose (n = 91)	2.0 mg/kg Dose (n = 84)
Age (yr)		
Mean	53.5	50.9
SD	9.9	11.7
Range	34–72	23–74
Weight (kg)		
Mean	82.7	84.6
SD	14.6	15.8
Range	52–123	46–127
Time from onset of pain to treatment (h)		
Mean	3.8	3.6
SD	1.5	1.4
Range	1.3–7.9	1.5–7.9
Gender		
Male	78 (85.7%)	76 (90.5%)
Infarct-related artery		
LCx	15 (16.4%)	11 (13.1%)
LAD	38 (41.8%)	30 (35.7%)
RCA	38 (41.8%)	43 (51.2%)

*There was no significant difference in any of the variables between the two groups. LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

Results

Baseline characteristics (Table 1). A total of 175 patients were entered into this study. Eighty-four patients were randomized to the 2 mg/kg dose regimen, and 91 to the 1.25 mg/kg dose arm. There were no differences in age, weight, time from onset of pain to treatment, gender or prevalence of infarct-related artery location between the groups. The mean time from onset of pain to treatment was 3.6 h in those receiving 2 mg/kg and 3.8 hours in those receiving 1.25 mg/kg, with a range of <2 h to almost 8 h in each group. The median dose of rt-PA was 100 mg (range 57 to 130) in those receiving 1.25 mg/kg. The group that received 2 mg/kg had a median dose of 145 mg (range 86 to 150). The time from initiation of therapy to the first arteriogram (labeled 60 min arteriogram) was 56 ± 8 min whereas the 90 min arteriogram was obtained at 90 ± 5 min.

Infarct-related vessel patency (Fig. 1). The group that received 2 mg/kg had an infarct-related artery patency rate of 65% (51 of 79, 95% confidence interval 52% to 73%) after 60 min of rt-PA infusion compared with 45% (40 of 89, 95% confidence interval 34% to 54%) in the group that received 1.25 mg/kg ($p = 0.01$). At 90 min, this trend continued, with the infarct-related artery patency being 84% (68 of 81, 95% confidence interval 73% to 89%) in the group that received 2

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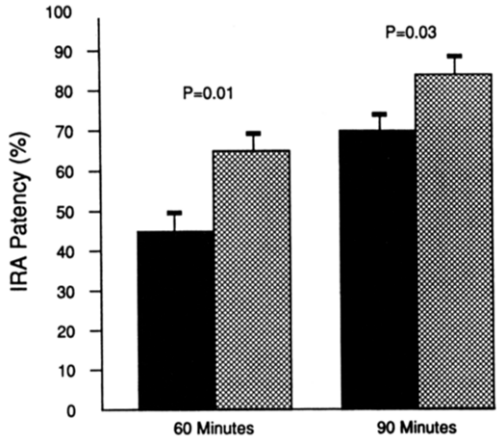


Figure 1. Comparison of infarct-related artery (IRA) patency in patients receiving 1.25 (**solid bars**) or 2 (**hatched bars**) mg/kg over 3 h of tissue-type plasminogen activator during acute myocardial infarction.

mg/kg compared with 70% 61 of 87, 95% confidence interval 59% to 78%) in the group that received 1.25 mg/kg ($p = 0.03$).

Effect of interventions on infarct-related artery patency (Table 2). The end point of this study was infarct-related artery patency before mechanical interventions after 90 min of rt-PA infusion. Coronary angioplasty or other interventions including bypass surgery were allowed after 90 min. Although it was not an end point of the study, the investigators considered it to be important to evaluate whether different doses of rt-PA had a positive or negative effect on subsequent interventions. The percent of patients treated with emergency coronary angioplasty in the groups receiving 1.25 or 2.0 mg/kg was equal. Patency of the infarct-related artery after emergency angioplasty was 88% and 89% in the group receiving 1.25 and 2 mg/kg, respectively. In patients with a residual closed infarct-related artery after unsuccessful recanalization by rt-PA, coronary angioplasty was attempted in 17 (65%) of the patients receiving 1.25 mg/kg and was successful in 11 (65%) of these. Angioplasty was performed in nine patients with a residual closed infarct-related artery in the group receiving 2 mg/kg, and was successful in six (67%). At discharge from the catheterization laboratory, there was a trend toward improved infarct-related artery patency in patients receiving 2 mg/kg compared with those receiving 1.25 mg/kg (91% versus 83%, respectively), although this difference did not achieve statistical significance ($p = 0.08$).

Angiographic reevaluation of these patients was not uniformly obtained before hospital discharge; however, there was a trend toward increased clinical evidence of reclosure (recurrent chest pain, further ECG changes, late enzyme increase or closed infarct-related artery at late angiography) in the group receiving 1.25 mg/kg compared with those receiving 2 mg/kg (22% versus 11%, $p = 0.045$). An equal number of patients were subjected to coronary artery bypass surgery either emergently after failed angioplasty or electively in each group and represented a small proportion (13%) of the total study group.

Table 2. Effect of Interventions on Infarct-Related Artery Patency

Treatment/Results	1.25 mg/kg Dose No.	(%)	2.0 mg/kg Dose No.	(%)	p Value
Treatment with emergent PTCA	58/91	(64)	54/84	(64)	NS
Patent IRA after emergency PTCA	51/58	(88)	48/54	(89)	NS
Patency after "rescue" PTCA	11/17	(65)	6/9	(67)	NS
Patent IRA at end of acute intervention	72/87	(83)	74/81	(91)	NS (0.08)
Angiographic or clinical evidence for IRA reclosure	14/50	(22)	6/50	(11)	0.045
Coronary artery bypass surgery before hospital discharge	12/91	(13)	11/84	(13)	NS

CCU = coronary care unit; IRA = infarct-related artery; PTCA = percutaneous transluminal coronary angioplasty.

Effect of rt-PA dose on coagulation variables. There was a significant decrease in fibrinogen level after treatment with the high dose (2 mg/kg) rt-PA regimen compared with the lower (1.25 mg/kg) dose, with fibrinogen decreasing to 115 ± 74 mg/dl in the group receiving 2 mg/kg compared with 174 ± 73 mg/dl in those receiving 1.25 mg/kg ($p < 0.0001$). This difference in fibrinogen levels was maintained at 24 h (Fig. 2). Similarly, the level of fibrinogen degradation products was significantly higher after rt-PA administration in the high dose group (32 μg/ml than in the standard dose group [8 μg/ml], $p = 0.0001$). This difference was also maintained at 24 h (Fig. 3).

Mortality (Table 3). Although death was not an end point of the study, it was monitored. The acute mortality rate in the group receiving 1.25 mg/kg was 7.7% compared with 4.8% in the group receiving 2 mg/kg. There was, however, an additional increment in cumulative mortality at 6 months to 11% in those receiving 1.25 mg/kg compared with 4.8% in the group receiving 2 mg/kg. These differences are statistically insignificant, although the sample size was not sufficient to detect small changes in mortality.

In patients with a patent infarct-related coronary artery, the acute mortality rate was 4.9% and 2.9%, respectively, in the groups receiving 1.25 and 2 mg/kg. At 6 months, among patients with an initially patent infarct-related artery, the mortality rate was 9.8% in those receiving 1.25 mg/kg compared with 2.9% in those receiving 2.0 mg/kg ($p = 0.15$). No death could be directly attributed to bleeding, although there was evidence for cerebral hemorrhage in two patients in the high dose group; neither of these two patients died as a result of the hemorrhage.

Bleeding complications (Table 4). A relatively small percent of patients had significant bleeding, with the majority of

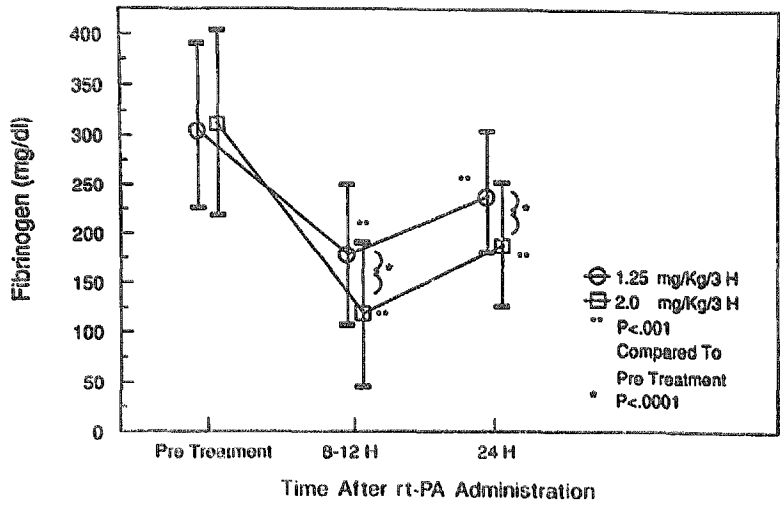
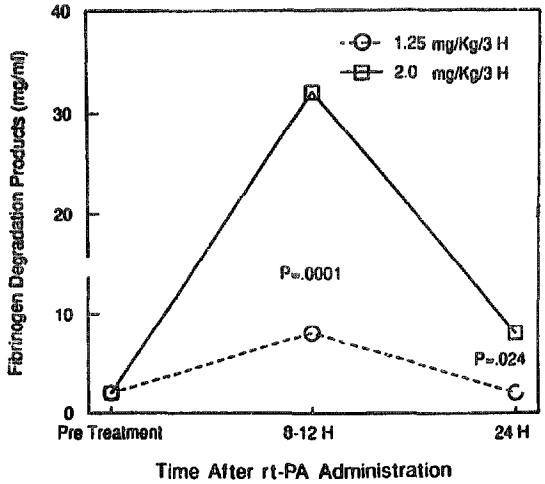


Figure 2. Fibrinogen levels after tissue-type plasminogen activator (rt-PA) administration in the two dosage groups.

episodes occurring at the catheterization site. There did not appear to be a correlation between rt-PA dose and bleeding complications, although the sample size was not sufficient to make this determination reliably. There were two patients with intracranial bleeding in the high dose group. One of the patients had a complicated clinical course including coronary reocclusion after angioplasty, cardiopulmonary resuscitation and emergency coronary bypass surgery. Death occurred 42 days after rt-PA treatment from multiple system failure. Computed tomography on day 17 revealed a cerebral hemorrhage that was thought to have occurred after surgery. A second patient developed a nonfatal cerebral hemorrhage 2.5 h after rt-Pa infusion that resulted in left-sided weakness. At 6 month follow-up study, minimal left arm weakness remained. There was no difference in transfusion requirements between the groups: 11 patients in the high dose group received 2 to 4 units of blood, whereas 10 patients in the low dose group received 1 to 3 units of blood.

Figure 3. Fibrin degradation products after tissue-type plasminogen activator (rt-PA) administration in the two dosage groups.



Discussion

Relation of rt-PA dose to coronary reperfusion. The results of this study suggest that higher doses of tissue-type plasminogen activator given in a weight-adjusted fashion with a greater proportion of drug administered during the first hour of infusion may result in higher patency rates compared with more traditional dosing schedules. The results of the TIMI Trial (8) supported an improved patency rate with higher doses of rt-PA. The (TAMI) Trial (9) came to a similar conclusion, suggesting that a higher, weight-adjusted first hour dose of rt-PA more rapidly produced recanalization and was associated with a higher 90 min patency rate.

In Figure 4, the 90 min infarct-related artery patency is compared with the rt-PA dose administered during the initial 90 min in TIMI-B and C, TAMI and the current study (high dose intravenous thrombolysis in myocardial infarction

Table 3. Mortality During Initial Hospitalization and at 6 Month Follow-Up Study

Mortality	1.25 mg/kg Dose No.	(%)	2.0 mg/kg Dose No.	(%)	p Value
Initial admission	7/91	(7.7)	4/84	(4.8)	0.54 (NS)
6 month follow-up	10/91	(11)	4/84	(4.8)	0.17 (NS)
Mortality in patients with patent IRA at end of acute intervention					
Initial admission	3/61	(4.9)	2/68	(2.9)	0.67 (NS)
6 month follow-up	6/61	(9.8)	2/68	(2.9)	0.15 (NS)

Abbreviations as in Table 2.

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Table 4. Bleeding Complications in 175 Patients

	All Reported Bleeding	Significant Bleeding*	
		2.0 mg/kg Dose	1.25 mg/kg Dose
Venipuncture site bleeding	73 (42%)	1 (1%)	2 (2%)
Gastrointestinal bleeding	10 (6%)	0 (0%)	1 (1%)
Hematuria	14 (8%)	1 (1%)	0 (0%)
Catheterization site hematoma	2 (1%)	0 (0%)	1 (1%)
Intracranial bleeding	2 (1%)	2 (2%)	0 (0%)
Retroperitoneal bleeding	2 (1%)	1 (1%)	1 (1%)
Death from bleeding	0 (0%)	0 (0%)	0 (0%)

*No significant differences between groups in any category.

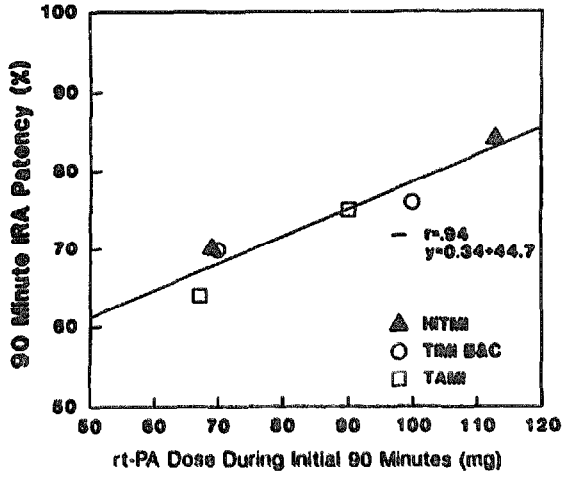

Figure 4. Comparison of tissue-type plasminogen activator (rt-PA) dose and infarct-related artery (IRA) patency after 90 min of rt-PA infusion in the current study (High dose Intravenous Thrombolysis in Myocardial Infarction [HITMI]), Thrombolysis in Myocardial Infarction (TIMI) B and C and Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) Trials.

[HITMI]). There is a linear relation between dose over the initial 90 min and 90 min infarct-related artery patency rate, with a correlation coefficient of 0.94.

Mechanisms of improved infarct-related artery patency. The possible mechanisms of improved patency include more severe fibrinogen depletion with higher doses of rt-PA, higher levels of fibrin degradation products after rt-PA and a direct effect of the higher rt-PA level itself. Topol et al. (10) suggested that fibrinogen depletion is dose-dependent with rt-PA and that rt-PA levels were inversely correlated with fibrinogen depletion, consistent with the reported findings in our study. If fibrinogen depletion alone was responsible, one would expect that similar results would be achieved with high doses of other activators. After administration of 1.5 million units of streptokinase, Collen et al. (11) reported that fibrin degradation product levels were higher and fibrinogen was lower than after rt-PA administration; however, reperfusion was more likely to occur after rt-PA administration. It would, therefore, appear that fibrinogen depletion and fibrin degradation products were not completely responsible for improved infarct-related arterial patency. Similar results were also reported by the TIMI investigators (12). These data suggest that the improved observed patency rate is a direct effect of higher levels of rt-PA.

Possible modification of reclosure risk. Gold et al. (13) in a fairly small study suggested that coronary reocclusion was not related to fibrinogen level, activated partial thromboplastin time or heparin dosage. However, they reported decreased reclosure with continued infusion of rt-PA, particularly in patients with >80% residual coronary artery stenosis. However, Verstraete et al. (14) believed that there was no difference in the reocclusion rate when rt-PA was not continued after the first hour. The TAMI investigators (15) suggested that when rt-PA and urokinase were infused simultaneously, the reocclusion rate was less but the initial patency rate was the same. Fibrin degradation products and fibrinogen depletion were much higher with the combination of rt-PA and urokinase; however, bleeding complications were no greater than with rt-PA alone. The TAMI report (15) supports the relation of decreased reclosure to either fibrinogen depletion or fibrin degradation products, or both, but does not address the issue of infusion duration. It has been suggested (16) that rt-PA itself promotes disaggregation of platelets in addition to its effect on dissolution of fibrin stands. Circulating fibrinogen degradation products have also been shown to inhibit platelet aggregation (17). Our study suggests that higher levels of rt-PA and circulating fibrin degradation products may be associated with both improved patency and diminished recurrent ischemia or postintervention reclosure.

Role of mechanical intervention. The TAMI investigators (15) suggested that the addition of "rescue" angioplasty in patients with residual total occlusion was associated with less abrupt reclosure when patients were treated with a combination of rt-PA and urokinase before angioplasty. Treatment with rt-PA alone followed by rescue angioplasty was associated with a higher mortality rate than treatment with rt-PA and urokinase (15). In our study, it appears that the risk of acute reclosure was no different when high dose rt-PA was utilized. However, the incidence of recurrent ischemic events after initial intervention tended to be less in patients treated with high dose rt-PA. It has been reported (18) that intravenous rt-PA resulted in infarct-related artery patency in approximately 75% of patients and that the addition of coronary angioplasty improved this patency rate to 94%. In our study, the addition of coronary angioplasty improved patency rates from 70% to 83% in the group that received 1.25 mg/kg and from 84% to 91% in the group that received 2 mg/kg rt-PA. Not all patients in our study with residual infarct-related artery occlusion were subjected to rescue coronary angioplasty. This difference in protocol may

account for the slightly different postintervention patency rates.

Risk of bleeding with higher doses of tissue-type plasminogen activator. The TAMI investigators (9) and others (19) have reported that administration of 150 mg of rt-PA does not result in an increased risk of intracranial bleeding. However, the TIMI investigators (8) suggested that higher doses of rt-PA may be associated with increased risk of intracranial bleeding. There were, however, substantial differences between the protocols used in the TAMI and TIMI studies. The TAMI investigators used a higher weight-adjusted dose of rt-PA during the first 60 min, and the remaining dose was administered over the next 5 h. In the TIMI study, 150 mg was given over 6 h and was not weight-adjusted. In our study, there were two episodes of intracranial bleeding in the group that received 2 mg/kg. One was discovered after open heart surgery in a patient with a complicated clinical course, and neither proved to be a fatal event. Furthermore, the mortality rate in the high dose group was less (although not significantly less) than that of the standard dose group. If the TIMI investigators were correct in assuming that higher doses of rt-PA resulted in a higher risk of intracranial bleeding, the question arises as to whether the higher risk was secondary to a more prolonged infusion and lack of modification of dose with respect to patient weight rather than a higher initial dose alone. It is possible that a higher weight-adjusted dose of rt-PA over 60 to 90 min, limiting the total dose to approximately 100 mg, would result in a higher infarct-related artery reperfusion rate and a lower reocclusion rate without a significant increase in bleeding risk. This "accelerated" mode of rt-PA delivery merits further investigation in a larger trial to confirm the improved patency rates and to ascertain the true risk of intracranial bleeding.

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